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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,805	12/13/2006	Martin Dugas	22329-US	3903

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EXAMINER	
AEDER, SEAN E	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,805	DUGAS ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *17-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *1 and 3-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The response filed on 12/19/07 to the restriction requirement of 10/31/07 has been received. Applicant has elected Group I, claims 1-16 for examination. Applicant further elects the species where the lower expression of sequence 1, 213907_at(EEF1E1), as defined by Table 1 and a higher expression of sequence 2, 234260_at, of Table 1 are indicative for the presence of denovo_AML when denovo_AML is distinguished from therapy-related AML. Because Applicant did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 1-27 are pending.

Claims 17-27 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 1-16 are currently under consideration.

Specification

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (pages 8, 19, 23, and 24, in particular). Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Claims 1-16 define the

invention by Affymetrix Identification numbers. Polynucleotide sequences corresponding to said Affymetrix Identification numbers are essential to practice the claimed invention, and the only disclosure of the sequences is made by references to published information outside of the specification. Therefore, information essential to practice the invention is incorporated by reference. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The amendment filed 2/20/07 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the submitted sequence listings. Applicant has not pointed-out support for the submitted sequence listings. While the originally filed application discloses that the invention involves many molecules that would have sequences, it is unclear whether the submitted sequences correspond to said molecules.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

Claim 1 is objected to because of an apparent typographical error. Claim 1 ends with two periods. Deleting one of said periods would obviate this objection. Proper correction is required.

Claims 3-6 are objected to for reciting the terms "preferably", "more preferably", "more preferred", and "most preferably". MPEP 2173.05(d) states that "Description of examples or preferences is properly set forth in the specification rather than the claims". Proper correction is required.

Claims 5-6 are objected to because of apparent typographical errors. There is an extra space between "5" and "%" in both claims. Deleting the space between "5" and "%" in both claims would obviate this objection. Proper correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims 2-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 1 recites a method for "distinguishing t(11q23)/MLL-positive leukemias from t(11q23)MLL negative leukemias" comprising determining the expression level of various markers; however, the claims do not particularly point out or distinctly claim what result indicates a leukemia is a t(11q23)/MLL-positive leukemia or what result indicates a leukemia is a t(11q23)MLL negative leukemia. See MPEP § 2172.01. The omitted steps are: correlating a particular result with a leukemia that is a t(11q23)/MLL-positive leukemia and correlating a particular result with a leukemia that is a t(11q23)MLL negative leukemia.

Claim 1 and dependent claims 2-16 are rejected because claim 1 contains the trademark/trade name Affymetrix. Where a trademark or a trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and the not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to describe polynucleotides and, accordingly, the identification/description is indefinite.

Claim 1 and dependent claims 2-16 are rejected because claim 1 recites a methods wherein "a lower expression" of at least one polynucleotide and "a higher expression" of at least one polynucleotide is indicative of a certain result; however, it is unclear *as compared to what* expression is determined to be "lower" or "higher". This renders the claim indefinite because the terms "lower" and "higher" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 3 recites the limitation "the label". There is insufficient antecedent basis for this limitation in the claim.

Claims 1, 4, and dependent claims 2, 3, and 5-16 are rejected because claims 1 and 4 recite methods wherein Tables found in the specification point-out what is claimed. 35 U.S.C. 112, second paragraph, requires the *claims* to particularly point-out and distinctly claim the subject matter. Further, MPEP 2173.05(s) states that claims are to be complete in themselves and incorporation by reference to a specific figure or table is permitted only where there is no practical way to define the invention in words. In the instant situation, there is a practical way to define the invention in words.

Claim 5 is rejected for reciting: "The method according to claim 1, wherein the expression level of markers expressed lower in a first subtype than in at least one second subtype, which differs from the first subtype, is a least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e.2-fold higher, preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold lower in the first subtype". It is unclear how marker of a second subtype (where markers are expressed higher) is preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold lower in the first subtype. The claim confusingly switches from describing a second subtype being 10-fold or 50-fold (higher?) than a first subtype (as "preferably at least 10-fold, more preferably at least 50-fold...") to a reference as to the first subtype being lower than something ("...at least 100-fold lower in the first subtype").

Claim 6 is rejected for reciting: "The method according to claim 1, wherein the expression level of markers expressed higher in a first subtype than in at least one second subtype, which differs from the first subtype, is at least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e. 2-fold higher, preferably at least 10-fold, more preferably at least 50-fold, and most preferably at least 100-fold higher in the first subtype. It is unclear how a marker of a second subtype which is **lower** than a first subtype "is at least 5 %, 10% or 20%, more preferred at least 50% or may even be 75% or 100%, i.e. 2-fold **higher**". Further, the claim confusingly switches from describing a second subtype being at least 5 %, 10% or 20%, more preferred at

least 50% or may even be 75% or 100%, i.e. 2-fold higher (than the first subtype?) to a reference to the first subtype being higher than something else.

Claim 11 is rejected for reciting "wherein at least one polynucleotide is in the form of a polypeptide, or a portion thereof". Polynucleotides are not polypeptides. It is unclear how a polynucleotide could be in the form of a polypeptide or a portion thereof.

Claim 12 and dependent claim 13 are rejected because claim 12 recites the limitation "the polypeptide". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because, the specification does not reasonably provide enablement for a method for distinguishing t(11q23)/MLL-positive leukemias from t(11q23)/MLL negative leukemias in just any sample comprising determining the expression level of polynucleotides comprising sequence 1, 213907_at(EEF1E1), of Table 1 and polynucleotides comprising sequence 2, 234260_at, of Table 1 wherein a lower expression of polynucleotides comprising sequence 1, 213907_at(EEF1E1), of Table 1, as compared to anything else, and higher expression of polynucleotides comprising sequence 2, 234260_at, of Table 1, as

compared to anything else, is indicative for the presence of denovo_AML when denovo_AML is distinguished from therapy-related AML.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to methods for distinguishing t(11q23)/MLL-positive leukemias from t(11q23)/MLL negative leukemias in just any sample comprising determining the expression level of polynucleotides comprising sequence 1, 213907_at(EEF1E1), of Table 1 and polynucleotides comprising sequence 2, 234260_at, of Table 1 wherein a lower expression of polynucleotides comprising sequence 1, 213907_at(EEF1E1), of Table 1, as compared to anything else, and higher expression of polynucleotides comprising sequence 2, 234260_at, of Table 1, as compared to anything else, is indicative for the presence of denovo_AML when denovo_AML is distinguished from therapy-related AML.

The specification *describe*s a method of determining whether leukemia sample comprises denovo_AML or therapy-related AML comprising determining the expression level of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1 and the expression level of polynucleotides comprising sequence 2, 234260_at, of Table 1

in said sample wherein: (1) leukemia samples with lower levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1, as compared to known levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1 in leukemia samples from patients with therapy-related AML, and higher levels of polynucleotides comprising sequence 2, 234260_at, of Table 1, as compared to known levels of polynucleotides comprising sequence 2, 234260_at, of Table 1 in leukemia samples from patients with therapy-related AML, are determined to comprise denovo_AML; and (2) leukemia samples with higher levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1, as compared to known levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1 in leukemia samples from patients with denovo_AML, and lower levels of polynucleotides comprising sequence 2, 234260_at, of Table 1, as compared to known levels of polynucleotides comprising sequence 2, 234260_at, of Table 1 in leukemia samples from patients with denovo_AML, are determined to comprise therapy-related AML. It is noted that Applicant has submitted a listing of sequences with SEQ ID NOs. However, it is unclear which polynucleotides said SEQ ID NOs correspond. Further, it is unclear which SEQ ID NO corresponds to sequence 1, 213907_at (EEF1E1), of Table 1 and it is unclear which SEQ ID NO corresponds to sequence 2, 234260_at, of Table 1. Therefore, due to the indefiniteness of what is meant by sequence 1, 213907_at (EEF1E1), of Table 1 and the indefiniteness of what is meant by sequence 2, 234260_at, of Table 1 one would not be able to perform said described method of determining whether leukemia sample comprises denovo_AML or therapy-related AML comprising determining the

expression level of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1 and the expression level of polynucleotides comprising sequence 2, 234260_at, of Table 1 in said sample wherein: (1) leukemia samples with lower levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1, as compared to known levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1 in leukemia samples from patients with therapy-related AML, and higher levels of polynucleotides comprising sequence 2, 234260_at, of Table 1, as compared to known levels of polynucleotides comprising sequence 2, 234260_at, of Table 1 in leukemia samples from patients with therapy-related AML, are determined to comprise denovo_AML; and (2) leukemia samples with higher levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1, as compared to known levels of polynucleotides comprising sequence 1, 213907_at (EEF1E1), of Table 1 in leukemia samples from patients with denovo_AML, and lower levels of polynucleotides comprising sequence 2, 234260_at, of Table 1, as compared to known levels of polynucleotides comprising sequence 2, 234260_at, of Table 1, are determined to comprise therapy-related AML.

The state of the prior art dictates that if a particular molecule is to be used as a surrogate for a particular diseased state, a particular expression pattern in a particular sample must be demonstrated to allow said particular expression pattern in said particular sample to be used to diagnose said particular diseased state. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful application.

Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points using a particular sample, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of correlation of a particular expression pattern of a particular molecule in a particular sample to a particular diseased state, one of skill in the art would not be able to predictably use said particular expression pattern of said particular molecule in said particular sample to diagnose said particular diseased state without undue experimentation.

Further, the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The sequences of the polynucleotides "sequence 1, 213907_at (EEF1E1), of Table 1" and "sequence 2, 234260_at, of Table 1" are critical or essential to the practice of the invention, but not included in the claims and are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). In order to practice the invention, one of skill has to know the polynucleotide sequence of "sequence 1, 213907_at (EEF1E1), of Table 1" and the polynucleotide sequence of "sequence 2, 234260_at, of Table 1". Note the objection to the specification above. An amendment accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application would obviate this part of rejection. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The level of unpredictability for the detection of any disease is quite high. Since the specification does not provide a definite description of the polynucleotides to be detected and because neither the specification nor the prior art provide evidence of a universal association between the claimed method and every type of sample or every determination of "higher expression" and "lower expression", a practitioner wishing to

practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA